2. SYNOPSIS

Name of Sponsor/Company: The Medicines Company **Name of Finished Product:** Inclisiran Injection **Name of Active Ingredient:** Inclisiran sodium	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: A Single Dose, Open Label, Parallel Group Study to Assess the Pharmacokinetics, Pharmacodynamics, And Safety of Inclisiran in Subjects with Hepatic Impairment Compared to Subjects With Normal Hepatic Function		
Principal Investigator: George J. Atiee, MD **Sub-Investigators:** Cynthia A. Zamora, MD Robert G. Bass, MD Nancy K. Hinitt, MD Elizabeth Crockett, MSN, FNP-BC Lydia Trejo, MSN, FNP-BC, RN Melissa L. Hearrell, MSN, APRN, FNP-C Jeff Bullock, MD		
Study center: Worldwide Clinical Trials Early Phase Services, LLC 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217		
Publications (reference): None		
Studied period: approximately 6 months Date first subject enrolled: 14 Nov 2018 Date last subject completed Day 60 End of Study Visit: 24 May 2019		**Phase of development: I**

Objectives:

The primary objective of the study was:

- To quantify the effect of different degrees of hepatic impairment (Child Pugh A and B compared to normal subjects) on the pharmacokinetics (PK) and the pharmacodynamics (PD) of inclisiran in order to develop dosing recommendations for subjects with hepatic impairment

The secondary objective was:

- Safety and tolerability of inclisiran in order to develop dosing recommendations for subjects with hepatic impairment

Study design:

Single-center, single-dose, open-label, parallel group study

Number of subjects (planned and analyzed):

Planned: Up to 40 subjects to provide a minimum of 18 to 24 evaluable (6 per hepatic impairment group and 6 to 12 matched subjects with normal hepatic function).

Enrolled: 28; 10 subjects with Child-Pugh A (mild hepatic impairment), 6 subjects with Child-Pugh B (moderate hepatic impairment), and 12 matched subjects (with normal hepatic function)

Diagnosis and main criteria for inclusion:

Male or female, between 18 and 79 years of age, inclusive, who weighed at least 50 kg (110 pounds) and had a body mass index (BMI) ≤40 kg/m^2 at Screening. Female subjects were not pregnant or lactating and were using a double-barrier method of birth control or were postmenopausal or surgically sterile. Subjects with normal hepatic function were in good health.

Eligible subjects were classified into three parallel study groups based upon their hepatic function at Screening. Subjects with normal hepatic function were dosed after completion of dosing of hepatic impaired subjects in order to ensure comparable demographics regarding age (±10 years), BMI (±20%), sex, and race (if possible).

Synopsis Table 1: Child-Pugh Assessment of Hepatic Function

	Points Scored for Observed Findings		
Parameter	**1**	**2**	**3**
Hepatic encephalopathy grade[a]	0	1 or 2[b]	3 or 4[b]
Ascites[c]	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	< 2	≥ 2 to ≤ 3	> 3
Serum albumin (g/dL)	> 3.5	≥ 2.8 to ≤ 3.5	< 2.8
International normalized ratio	< 1.7	≥ 1.7 to ≤ 2.3	> 2.3

[a] Grade 0: normal consciousness, personality, neurological examination, or electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second (cps) waves.
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, or slow 2 to 3 cps delta activity.

[b] Subject with hepatic encephalopathy of Grade 2 or above were not admitted into the study.

[c] Absent: No ascites is detectable by manual examination or by ultrasound investigation, if ultrasound investigation is performed.
Slight: Ascites palpation doubtful, but ascites measurable by ultrasound investigation, if performed.
Moderate: Ascites detectable by palpation and by ultrasound investigation, if performed.
Severe: Necessity of paracentesis; does not respond to medication treatment. Subject would not be admitted into the study.

Synopsis Table 2: Classification of Hepatic Function Study Groups

Population	**Child-Pugh Assessment**
Severe hepatic impairment[a]	Class C (10 to 14 points)
Moderate hepatic impairment	Class B (7 to 9 points)
Mild hepatic impairment	Class A (5 to 6 points)
Normal hepatic function	--

[a] Subjects with severe hepatic impairment were not enrolled in this study.

Test product, dose and mode of administration, batch number:

Inclisiran Injection

Dose = Inclisiran sodium 300 mg/1.5 mL, (equivalent to 284 mg inclisiran) was administered as a single, subcutaneous injection on Day 1

Batch: B180004

Duration of treatment: Single dose

Criteria for evaluation:

Pharmacodynamic: Pharmacodynamic assessments measured the effects of inclisiran on total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), calculated low-density lipoprotein cholesterol (LDL-C, beta-quantification was to be performed if TG was high or LDL-C was low), and proprotein convertase subtilisin kexin type 9 (PCSK9) protein levels at baseline, 4 hours, 48 hours, 96 hours (Day 5), 144 hours post dose (Day 7), Day 30 (± 3 days), and Day 60 (± 3 days).

Safety: Adverse events (AEs), serious adverse events (SAEs), vital signs, electrocardiogram (ECG) assessments, physical examination assessments, and clinical laboratory values (hematology, coagulation, biochemistry, and urinalysis) were collected.

Pharmacokinetic: Inclisiran PK was determined by noncompartmental analysis with Phoenix WinNonlin (Certara USA, Inc., version 6.3). Pharmacokinetic assessments included maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), elimination half-life ($t_{1/2}$), apparent volume of distribution based in the terminal phase (V_d/F), apparent total clearance (CL/F), area under the curve (AUC) of the plasma concentration from time 0 to 24 hours (AUC_{0-24}), AUC from time 0 to 48 hours (AUC_{0-48}), AUC from time 0 to time of last measurable concentration (AUC_{last}), AUC to infinity (AUC_{inf}), amount excreted unchanged in urine (Ae), percent of unchanged drug in urine (f_e), and renal clearance (CL_R).

Statistical methods:

The sample size of a minimum 18 to 24 evaluable subjects (6 per hepatic function group and 6 to 12 matching subjects with normal hepatic function) was chosen based on feasibility and clinical judgment to provide adequate precision in describing the effect of hepatic impairment on inclisiran PK.

The primary analysis planned for this study was to evaluate the PK of inclisiran after a single dose in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function (control group). The primary PK parameters AUC_{inf}, AUC_{last}, and C_{max} were analyzed using a mixed-model analysis of variance (ANOVA) to estimate the ratio of the geometric means and the corresponding 90% confidence interval (CI) of the ratio between each level of impaired hepatic function versus the control group. In the ANOVA, hepatic impairment group was a fixed effect. These analyses were performed on the log-transformed PK parameters (AUC_{inf}, AUC_{last}, and C_{max}). In addition, mathematical modeling of relationships between hepatic function and appropriate PK parameters may have been conducted.

Plasma concentrations and PK parameters were summarized by hepatic function using descriptive statistics (number, arithmetic mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum).

Descriptive statistics were provided for demographic and baseline parameters. Descriptive statistics included means, medians, standard deviations, minimum, and maximum for continuous variables, as well as frequency and percentage for categorical variables. No statistical hypothesis testing was planned for demographic and baseline parameters. However, when appropriate, p-values and two-sided 95% CIs may have been estimated for non-PK parameters.

Summary tables and listings of safety data, including AEs, laboratory results, PK data, PD data, ECGs, and vital signs were provided.

Methodology:

Matched subjects with normal hepatic function were enrolled on a 1 to 1 basis and were not matched to more than one hepatically impaired subject within each hepatic function group; however, subjects with normal hepatic function could be matched to a subject from each hepatic impairment group.

Informed consent was obtained from subjects meeting the selection criteria before the initiation of any study specific procedures.

Screening took place within 30 days prior to dosing. Eligible subjects were admitted to the clinical research unit (CRU) on Day -1, the day before investigational product administration, and remained confined at the CRU until 48 hours post dose. Safety evaluations were conducted during a visit on Day 60 (± 3 days), including lipid panel levels, AEs, SAEs, concomitant medications, and safety laboratory assessments.

After the Day 60 visit, subjects were to be followed every 60 days until LDL-C levels returned to within 50% of the absolute change from baseline or until Day 180 (± 3 days), whichever occurred first. At each visit, lipid panel levels, AEs, SAEs, concomitant medications, and safety laboratory assessments (Days 60 [± 3 days] and 180 [± 3 days], only) were to be collected

Serial blood samples for analysis of inclisiran concentration were collected at the following timepoints: before injection (0 hour) and 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 96, and 144 hours and Day 14 (± 1 day) and Day 30 (± 3 days) post-dose. Only pooled urine samples were used for PK analysis. Samples were collected after dose at 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hour post-dose intervals.

RESULTS:

An analysis was conducted following the End of Study visit (Day 60 ±3 days); this report includes data up to the Day 60 visit including all relevant pharmacokinetic, pharmacodynamic, and safety findings.

A second analysis and report addendum will be provided which will include all follow-up data

collected through Day 180.

PHARMACOKINETIC RESULTS:

The PK report is provided separately in Section 16.1.13.1.

PHARMACODYNAMIC RESULTS:

LDL-C, PCSK9, and TC decreased from Baseline to Day 60 in all groups. The decreases were less pronounced in the group of subjects with moderate hepatic impairment. Among the subjects with moderate impairment, those with the greatest level of impairment (CP score of 9) had the least response to inclisiran.

Changes in TG levels from Baseline to Day 60 varied among the three groups and HDL-C levels increased in all groups.

In general, the effect of inclisiran on PD parameters decreased with moderate hepatic impairment.

SAFETY RESULTS:

There were no deaths or TEAEs leading to subject discontinuation.

One severe TESAE (seizure) was reported for a subject with moderate hepatic impairment. The TESAE was not related to the study treatment. One moderate TEAE (vomiting) was reported. All other TEAEs were mild.

The most commonly reported TEAE was cough (3 events: 2 reported for 2/10 (20.0%) subjects with mild hepatic impairment and 1 event reported for 1/6 (16.7%) subjects with moderate hepatic impairment).

Other commonly reported TEAEs were diabetes mellitus (2 events, reported by 2/10 [20.0%] subjects with mild hepatic impairment); dysuria (2 events, reported by 1/10 [10.0%] subjects with mild hepatic impairment and 1/12 [8.3%] subjects with normal hepatic function); injection site pain (2 events, reported by 2/10 [20%] subjects with mild hepatic impairment); pruritus generalized (2 events, 1 reported by 1/10 [10%] subjects with mild hepatic impairment and 1 by 1/6 [16.7%] subjects with moderate hepatic impairment); and vomiting (2 events, reported by 2/10 [20.0%] subjects with mild hepatic impairment).

All treatment-related TEAEs occurred in subjects with mild or moderate hepatic impairment.

Although clinically significant (CS) clinical laboratory test results were reported for several subjects, none of the results led to a TEAE.

No CS findings in ECGs or vital signs were reported. There were no unusual or unexpected TEAEs.

In general, the effects of inclisiran on PD parameters were similar in subjects with normal hepatic function and mild hepatic impairment but were decreased in subjects with moderate hepatic impairment. Subjects with moderate hepatic impairment and a CP score of 7 had PD results similar to the subjects with mild hepatic impairment and normal hepatic function. The effects of inclisiran were observed to a lesser degree in subjects with moderate hepatic impairment and a CP score of 9.

CONCLUSION:

No dose adjustment of inclisiran is recommended in subjects with mild or moderate hepatic impairment based on the study results. Overall, inclisiran was well-tolerated when administered as a single, subcutaneous 300 mg dose to subjects with mild hepatic impairment, moderate hepatic impairment, and normal hepatic function. The PK conclusions are provided separately in Section 16.1.13.

Date of the report: 27 November 2019

Sponsor

Novartis

Novartis Study Code

MDCO-PCS-18-02 (orion6)

EudraCT Number

Not applicable

Swiss Authorization Date and Authorization number

Authorization Date: 09 September 2021

Authorization Number: 67836

Information on comparators, particularly dosage, route of administration, batch number

Not applicable